C–H Activation

DOI: 10.1002/ange.201207770

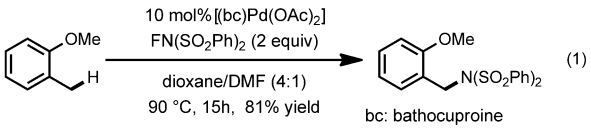
# Ether-Directed *ortho*-C–H Olefination with a Palladium(II)/ Monoprotected Amino Acid Catalyst**

*Gang Li, Dasheng Leow, Li Wan, and Jin-Quan Yu**

Cyclopalladation reactions promoted by strong $\sigma$-chelation have served as a fruitful platform for studying and developing redox chemistry to establish catalytic cycles for C–H functionalization processes.[1] However, these well-established C–H activation reactivities have several limitations from the viewpoint of both catalysis and synthetic applications.[1f] First, the cyclopalladated intermediates are thermodynamically stable and less reactive in the subsequent functionalization step, thereby making early discovery of suitable conditions for a diverse range of catalytic reactions difficult. Second, the substrates are typically limited to molecules containing nitrogen-, sulfur-, or phosphorus-chelating groups.[1a] Third, the strongly coordinating directing groups either outcompete ligands for vacant coordination sites or dominate the electronic properties of the metal centers, both of which are not desirable for developing ligand-controlled reactions. In response to these challenges, we and others have recently established weak coordination as a powerful means for directing catalytic C–H activation with $Pd^{II}$, $Rh^{III}$, and $Ru^{II}$ catalysts.[2–3] The interplay between a suitable ligand and these types of weak coordination on $Pd^{II}$ centers was also shown to accelerate C–H activation.[4] Herein, we demonstrate for the first time that monoprotected amino acid ligands (MPAA) promote ether-directed C–H olefination,[1e] which provides a method to functionalize readily available arylethyl ethers to afford novel cinnamate derivatives.

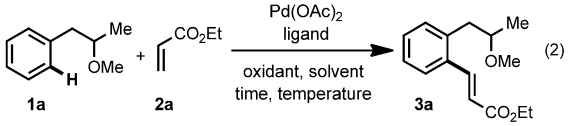
Ether is one of the most common functional groups in natural products and drug molecules.[5] The development of ether directed C–H functionalization reactions would be very useful and important. However, such reports are very rare in literature,[6,7] presumably owing to the poor coordination of ethers to late transition metal centers. To our knowledge, only one example of ether-directed C–H functionalization with a $Pd^{II}$ catalyst is documented to date, and it is arylether-directed benzylic C–H amidation reported by Álvarez and Muñiz et al. [Eq. (1)].[6a] While this reaction is an intriguing example of using arylether directing groups to promote activation of benzylic C–H bonds, the use of simple alkylethers to direct aryl C–H activation via a six-membered cyclopalladation represents a distinct and unanswered challenge. Since alkylethers are widespread in natural products and drug molecules,[5] we set out to develop C–H activation reactions using a combination of weak coordination of the alkylether moiety and ligand acceleration[2h] to provide a new method for the functionalization of a major class of ethers, namely arylethyl ethers [Eq. (2)].

Arylether-directed benzylic C–H activation:[6a]




(1)

Alkylether-directed aryl C–H activation:




(2)

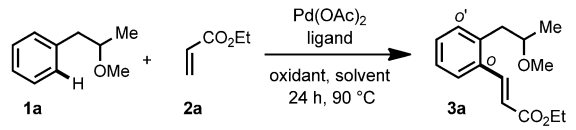
Taking into consideration the weakly coordinating ability of the ether moiety, we began to develop the olefination of ether **1a** using a weakly coordinating solvent hexafluoroisopropanol (HFIP).[2h] Thus a mixture of ether **1a** (0.2 mmol), ethyl acrylate **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), and $Ag_2CO_3$ (0.4 mmol) was stirred in HFIP (2 mL) under 90 °C for 24 h (Table 1, entry 1). $^1$H NMR analysis detected the formation of the mono-olefinated product **3a** in 11% yield. Guided by previous studies on $Pd^{II}$-catalyzed C–H activation using MPAA ligands,[2h,4] we screened these ligands and observed significant improvement of the reaction with several ligands (Table 1, entries 2–4).[8] The olefinated products were formed in 92% total yield (mono/di = 1.9/1) when Ac-Gly-OH was used (Table 1, entry 4). Other solvents except $CF_3CH_2OH$ drastically decreased the yields (Table 1, entries 5–7). Among the oxidants tested, $Ag_2CO_3$ was shown to be the most effective one, which was consistent with our previous report on $Pd^{II}/Pd^0$ catalysis (Table 1, entries 8–11).[9] Notably, the use of $O_2$ as the terminal oxidant was also possible with a catalytic amount of $Cu(OAc)_2$ (Table 1, entry 12). To improve the mono-selectivity, reaction conditions were further optimized (Table 1, entries 13–16). Either lowering the reaction temperature or stopping the reaction at lower conversion led to improved mono-selectivity while

[*] Dr. G. Li, Dr. D. Leow, L. Wan, Prof. Dr. J.-Q. Yu
Department of Chemistry, The Scripps Research Institute (TSRI)
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: yu200@scripps.edu
Homepage: http://www.scripps.edu/chem/yu

[**] We gratefully acknowledge The Scripps Research Institute, the National Institutes of Health (NIGMS, 1 R01 GM084019-04), Amgen, Novartis, and Eli Lilly for financial support. We also thank the Agency for Science, Technology and Research (A*STAR) Singapore for a postdoctoral fellowship (D.L.). L.W. is a visiting student from Nanjing University of Science and Technology, sponsored by the China Scholarship Council.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207770.

***Table 1:*** Optimization of reaction conditions.[a,b]

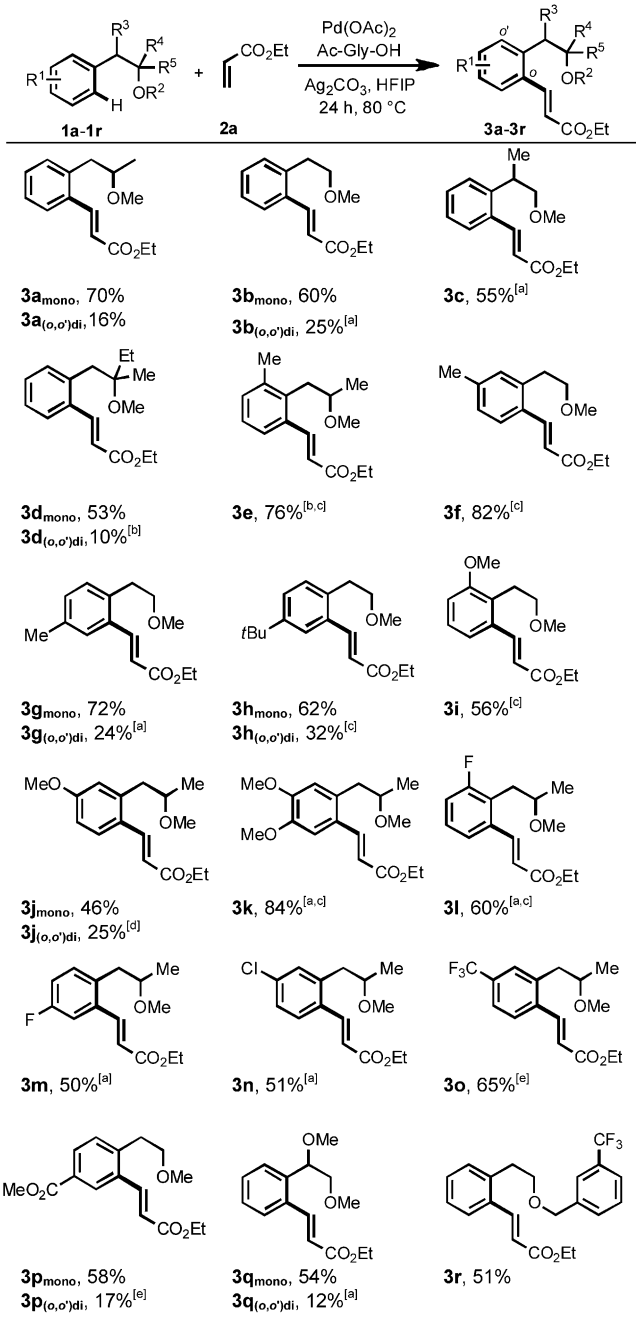



| Entry | Ligand | Solvent | Oxidant | Yield [%] (mono/di) |
|---|---|---|---|---|
| 1 | – | HFIP | $Ag_2CO_3$ | 11 (1/0) |
| 2 | Ac-Ile-OH | HFIP | $Ag_2CO_3$ | 38 (11.7/1) |
| 3 | Ac-Ala-OH | HFIP | $Ag_2CO_3$ | 73 (4.6/1) |
| **4** | **Ac-Gly-OH** | **HFIP** | **$Ag_2CO_3$** | **92 (1.9/1)** |
| 5 | Ac-Gly-OH | *tert*-amyl-OH | $Ag_2CO_3$ | trace |
| 6 | Ac-Gly-OH | $CF_3CH_2OH$ | $Ag_2CO_3$ | 69 (6.7/1) |
| 7 | Ac-Gly-OH | DCE | $Ag_2CO_3$ | trace |
| 8 | Ac-Gly-OH | HFIP | AgOAc | 86 (1.7/1) |
| 9 | Ac-Gly-OH | HFIP | $Ag_2O$ | 4 (1/0) |
| 10 | Ac-Gly-OH | HFIP | $Cu(OAc)_2$ | 13 (1/0) |
| 11 | Ac-Gly-OH | HFIP | $O_2$ (1 atm) | 7 (1/0) |
| 12[c] | Ac-Gly-OH | HFIP | $O_2/Cu(OAc)_2$ | 41 (20/1) |
| **13[d]** | **Ac-Gly-OH** | **HFIP** | **$Ag_2CO_3$** | **90 (4.3/1)** |
| 14[e] | Ac-Gly-OH | HFIP | $Ag_2CO_3$ | 73 (5.6/1) |
| 15[f] | Ac-Gly-OH | HFIP | $Ag_2CO_3$ | 90 (2.6/1) |
| 16[g] | Ac-Gly-OH | HFIP | $Ag_2CO_3$ | 71 (3.7/1) |

[a] Conditions: **1a** (racemic, 0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), oxidant (0.4 mmol), solvent (2 mL), 90°C, 24 h, in a 35 mL sealed tube. [b] Total yield of (*o*)-mono- and (*o*,*o*′)-di-olefinated products determined with $CH_2Br_2$ as internal standard, ratios of mono/di are in brackets. [c] $O_2$ (1 atm), $Cu(OAc)_2$ (0.1 mmol), 36 h. [d] 80°C. [e] 12 h. [f] 18 h. [g] **2a** (0.2 mmol). Ac = acetyl, Ile = L-isoleucine, Ala = L-alanine, Gly = glycine, *tert*-amyl-OH = *tert*-amyl alcohol, DCE = 1,2-dichloroethane.

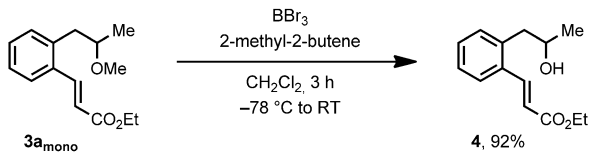
maintaining good yields (Table 1, entries 13,14). The mono- and di-olefinated products were easily separated by silica gel chromatography.

To examine the substrate scope of this reaction, we methylated a wide range of readily available arylethanols with MeI to give the corresponding ethers. Ethers derived from primary, secondary, and tertiary alcohols were olefinated to give the desired cinnamates in 55–96% yields (**3a**–**h**; Scheme 1). It is worth noting that the corresponding hydroxy-directed olefination reaction with primary and secondary arylethyl alcohols suffered from partial oxidation of the alcohols to aldehydes and ketones and decomposition of the substrates, thereby resulting in an unproductive reaction.[4b] Both electron-donating (**3i**–**k**) and electron-withdrawing groups (**3l**–**p**) on the arenes were tolerated. Except for a highly reactive arene (**3j**), *meta*-substituted arenes were typically olefinated in greater than 95% monoselectivities (**3f**, **3k**, and **3o**). Olefination of the methyl ether of the diol also proceeded to give **3q** in 66% total yield. Not surprisingly, the replacement of the methyl group by a benzyl group in the ether substrates resulted in olefination on both arenes to give an inseparable mixture. However, olefination of *meta*-trifluoromethylbenzyl ether proceeded selectively to give the desired product **3r** in 51% yield, suggesting alkylethers other than methyl ethers are also reactive. Moreover, when a hydroxy group is desired for further functionalization, the methyl ether products can be demethylated with $BBr_3$ by using a literature procedure (Scheme 2).[10]

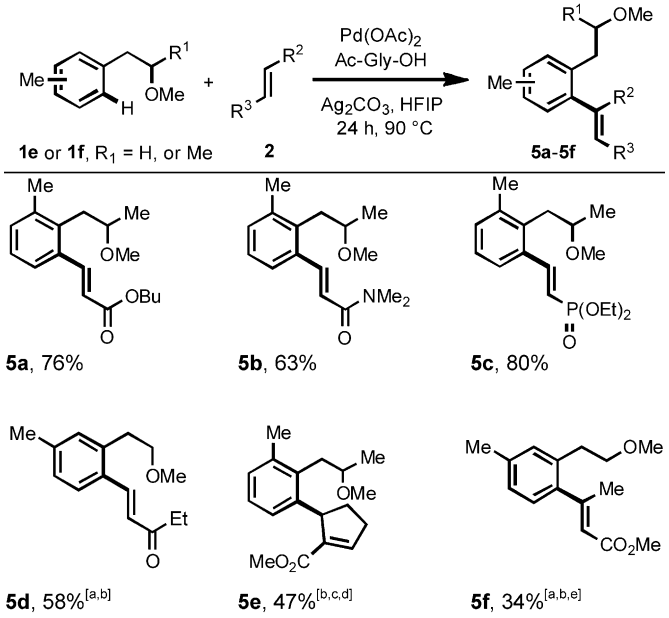



***Scheme 1.*** $Pd^{II}$-catalyzed *ortho*-C–H olefination of ethers. Conditions: **1** (racemic, 0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), $Ag_2CO_3$ (0.4 mmol), HFIP (2 mL), 80°C, 24 h, in a 35 mL sealed tube. Yields of isolated *ortho*-olefinated products are given; *meta*- or *para*-olefinated regioisomers are also detected as minor products; for **1c**, **1m**, and **1r**, (*o*,*o*′)-di-olefinated products were observed but not isolated; see the Supporting Information for details. [a] 48 h. [b] **2a** (0.25 mmol). [c] 90°C. [d] 100°C. [e] See the Supporting Information for condition variations.

The scope of the olefin coupling partners was also examined (Scheme 3). Olefination of ether **1e** or **1f** with various olefin coupling partners such as α,β-unsaturated ester, amide, phosphonate, and ketone gave the corresponding cinnamates in good yields (**5a**–**5d**). Although the di- or tri-substituted olefins are usually not compatible with *ortho*-C–H




***Scheme 2.*** Demethylation of the olefinated product.




***Scheme 3.*** Scope of olefins. Conditions: **1** (racemic, 0.2 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), $Ag_2CO_3$ (0.4 mmol), HFIP (2 mL), 90°C, 24 h, in a 35 mL sealed tube. Yields of *ortho*-olefinated products are given; *meta*- or *para*-olefinated regioisomers are also detected as minor products; see the Supporting Information for details. [a] **2** (0.4 mmol). [b] 48 h. [c] $Pd(OAc)_2$ (15 mol%) and Ac-Gly-OH (30 mol%) used. [d] Only one diasteromer isolated; relative configuration of **5e** not determined. [e] 100°C.

olefination,[4a] modest yields (47%, 34%) were obtained with the ether directing group (**5e**, **5f**).

In summary, we have developed an ether-directed C–H olefination with $Pd^{II}$/MPAA catalysts, thereby further demonstrating the potential of weak coordination as a useful tool for promoting C–H activation. This reaction can provide a new method for chemically modifying readily available and synthetically useful ethers. We are currently developing the asymmetric variant of this reaction by tuning the chiral MPAA ligands.

Received: September 26, 2012
Revised: November 27, 2012
Published online: December 13, 2012

**Keywords:** C–H activation · ether · olefination · palladium · weak coordination

[1] For selected reviews, see: a) A. D. Ryabov, *Synthesis* **1985**, 233; b) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; e) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170; f) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788.

[2] For examples of $Pd^{II}$-catalyzed C–H functionalizations directed by weak coordination, see: a) D.-H. Wang, X.-S. Hao, D.-F. Wu, J.-Q. Yu, *Org. Lett.* **2006**, *8*, 3387; b) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452; c) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460; d) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680; e) P. Gandeepan, K. Parthasarathy, C.-H. Cheng, *J. Am. Chem. Soc.* **2010**, *132*, 8569; f) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1466; g) P. Gandeepan, C.-H. Cheng, *J. Am. Chem. Soc.* **2012**, *134*, 5738; h) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.

[3] For advances in $Rh^{III}$- and $Ru^{II}$-catalyzed C–H activation reactions directed by weak coordination, see: a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; b) For rhodium-catalyzed oxidative coupling of benzyl alcohols with alkynes, see: K. Morimoto, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 9548; c) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096; *Angew. Chem. Int. Ed.* **2011**, *50*, 1064; d) S. H. Park, J. Y. Kim, S. Chang, *Org. Lett.* **2011**, *13*, 2372; e) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153; f) K. Padala, M. Jeganmohan, *Org. Lett.* **2011**, *13*, 6144; g) For an early example of $Ru^0$-catalyzed C–H bond functionalization of acetophenones, see: S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.

[4] a) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137; b) Y. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916; c) Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967; d) H. X. Dai, A. F. Stepan, M. S. Plummer, Y. H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222; e) K. M. Engle, P. S. Thuy-Boun, M. Dang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 18183; f) C. Huang, B. Chattopadhyay, V. Gevorgyan, *J. Am. Chem. Soc.* **2011**, *133*, 12406; g) P. Novák, A. Correa, J. Gallardo-Donaire, R. Martin, *Angew. Chem.* **2011**, *123*, 12444; *Angew. Chem. Int. Ed.* **2011**, *50*, 12236.

[5] T. Henkel, R. M. Brunne, H. Müller, F. Reichel, *Angew. Chem.* **1999**, *111*, 688; *Angew. Chem. Int. Ed.* **1999**, *38*, 643.

[6] a) For phenylether-directed amidation of benzylic C–H bonds with $Pd^{II}$ catalyst, see: Á. Iglesias, R. Álvarez, Á. R. de Lera, K. Muñiz, *Angew. Chem.* **2012**, *124*, 2268; *Angew. Chem. Int. Ed.* **2012**, *51*, 2225; b) For scandium-catalyzed silylation of aromatic C–H bonds of phenylethers, see: J. Oyamada, M. Nishiura, Z. Hou, *Angew. Chem.* **2011**, *123*, 10908; *Angew. Chem. Int. Ed.* **2011**, *50*, 10720.

[7] a) For acetal-directed C–H borylation of arenes with iridium catalyst, see: S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawamura, *J. Am. Chem. Soc.* **2009**, *131*, 5058; b) For iridium-catalyzed C–H borylation of secondary C–H bonds of cyclic ethers, see: C. W. Liskey, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 12422.

[8] Considering the possibility of partial kinetic resolution in the presence of chiral ligands, we measured the enantiomeric excess (*ee*) of mono-olefinated product, and observed low *ee* values: 5.6% *ee* with Ac-Ile-OH and 3.3% *ee* with Ac-Ala-OH. We thank one of the referees for raising this question.

[9] R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510.

[10] Y. Tang, K. P. Cole, G. S. Buchanan, G. Li, R. P. Hsung, *Org. Lett.* **2009**, *11*, 1591.